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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,521	01/31/2002	John Bertin	07334-334001	3688

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,521	BERTIN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11 and 21-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,4,6,21 and 34* is/are allowed.

6)☒ Claim(s) *5,7,22-33 and 35-44* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicants election without traverse of the species of SEQ ID NO:6.

2. Claims 2, 3, 8, 10 and 12-20 have been canceled. Claims 1, 4-7 and 11 have been amended. Claims 21-44 have been added. Claims 1, 4-7, 11 and 21-44 are pending and examined on the merits.

3. Acknowledgement is made of applicants claim to an earlier effective filing date via provisional applications 60/265,231, filed January 31, 2001 and 60/318,645, filed September 10, 2001. After review of each of the provisional applications, it is noted that only the '645 application provides support for the instant SEQ ID NO:6 (pyrin 5) but does not provide support for nucleic acids encoding a nucleotide sequence which is 85%, 95% or 98% identical to SEQ ID NO:6 or nucleic acid sequences which hybridize under conditions of instant claim 5 to SEQ ID NO:5. Accordingly, claims 1, 2, 6, 7, 11, 21, 30-34, 36, 41-44 will be given the priority date of September 10, 2001 consistent with the '645 application and claims 5, 22-29, 35, 37-40 will be given the instant filing date of January 31, 2002.

4. The specification is objected to for containing numerous blank spaces after multiple occurrences of "ATCC".

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5, 22-33, 35-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 5 is drawn to an isolated nucleic acid molecule that hybridizes to a nucleotide sequence consisting of SEQ ID NO:5 under conditions of incubation at 45 degrees in 6.0X SSC followed by washing in 0.2X SSC/0.1% SDS at 65 degrees. Claims 28 and 29 embody the nucleotide sequence of claim 5 wherein the sequence comprises at least 600 and at least 1000 nucleotides, respectively. Claim 30 is drawn to an isolated nucleic acid sequence that encodes a polypeptide comprising amino acid residues 1-91, 188-506 or 688-1056 of SEQ ID NO:6. Claims 31-33 embody the nucleic acid of claim 30 wherein the polypeptide comprises amino acids 1-91, 188-506 and 688-1056 of SEQ ID NO:6, respectively. Claims 35, 37, 38-40 are dependent on the identity of the nucleic acids of claim 22. Claims 36, 41-44 are dependent upon the identity of the isolated nucleic acids of claim 30.

Claim 22 is drawn to an isolated nuclei acid comprising a nucleotide sequence that encodes an amino acid sequence which is at least 85% identical to SEQID NO:6. Claims 23 and 24 embody the nucleic acid of claim 22 wherein the amino acid sequence is at least 95% and 98% identical to the sequence of SEQ ID NO:6, respectively. Claim 25 is drawn to an isolated nucleic acid sequence that is at least 95% identical to SEQ ID NO:5. Claims 26 and 27 embody the isolated nucleic acid sequence of SEQID NO:5 wherein the nucleotide sequence is at least 95% and 98% identical to the sequence of SEQ ID NO:5, respectively.

Claims 5, 28 and 29 are drawn to a genus of isolated nucleic acids which hybridizes to SEQ ID NO:5 under conditions of incubation at 45 degrees in 6.0X SSC followed by washing in 0.2X SSC/0.1% SDS at 65 degrees. The genus of nucleic acids are not limited by the functional attributes of what is encoded by the hybridizing nucleic acid. Thus, the genus is variant, encompassing nucleic acids which encoded mutant, truncated and allelic variants of SEQ ID NO:5. The specification sets forth SEQ ID NO:5 as encoding SEQ ID NO:6. With the exception of degenerate coding sequences of SEQ ID NO:5, the specification does not provide adequate written description for the genus of nucleic acids which would hybridize under the recited conditions to SEQ ID NO:5 because the genus includes nucleic acids which encode proteins having widely different functional attributes for the instant SEQ ID NO:6. The specification does not provide adequate written description for allelic variants of SEQ ID NO:5

because it is excepted in the art that the structure and function of a wild type polynucleotide does not provide a nexus to the structure or function of an allelic variants because said the structure of an allelic variant arises from a mutational event, therefore the structure and function of said allelic variant cannot be predicted from the structure of a wild-type polynucleotide.

Claims 30-33, are drawn to isolated nucleic acids which minimally comprise a domain of SEQ ID NO:6 selected from the group consisting of the pyrin domain of SEQ ID NO:6 (amino acid residues 1-91), the NBS domain of SEQ ID NO:6 (amino acid residues 188-506 of SEQ ID NO:6) and the LRR domain of SEQ ID NO:6 (amino acid residues 688-1056 of SEQ ID NO:6). The claims are drawn to a genus of nucleic acids which encode proteins which minimally comprise a pyrin, NBS or LRR domain of SEQ ID NO:6. The genus of nucleic acids encompassed by the claims is highly variant because numerous structural alterations are tolerated in the proteins encoded by the nucleic acids and the genus tolerated members which encode proteins having numerous functional attributes which differ from those of SEQ ID NO:6. The disclosure of polynucleotide encoding SEQ ID NO:6 does not adequately describe the claimed genus which includes nucleic acids encoding protein which differ both structurally and functionally from the instant SEQ ID NO:6.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of the isolated nucleic acids which hybridize to SEQ ID NO:5, the isolated nucleic acids which encode a proteins which is 85%, 95% and 98% identical to SEQ ID NO:6, isolated nucleic acids which are 98%, 95% or 85% identical to SEQ ID NO:5, or isolated nucleic acids encoding proteins which minimally comprise residues 1-91, 188-506 or 688-1056 of SEQ ID NO:6 per Lilly by structurally describing a representative number of the variant proteins or the variant nucleic acids or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the variant nucleic acids, or the nucleic acids encoding a proteins which minimally comprises domains of SEQ ID NO:6 in a manner that

satisfies either the Lilly or Enzo standards. Although the specification discloses the full length pyrin 5 as SEQ ID NO:6 and the pyrin, NBS and LRR domains of SEQ ID NO:6 this does not provide a description of the variant nucleic acids encoding variant SEQ ID NO:6, nor does it provide an adequate written description of the isolated nucleic acids encoding proteins which minimally comprise said domains of pyrin-5 The specification also fails to describe the variant nucleic acids and the nucleic acids encoding proteins which minimally comprise domains of SEQ ID NO:6 by the test set out in Lilly. The specification describes only SEQ ID NO:6 as pyrin-5, therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

One of skill in the art would reasonable conclude that applicant was not in possession of the claimed genuses.

7. Claims 7, 38, 39, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 7 is drawn to the host cell containing the expression vector of claim 6. Claim 38 is drawn to a host cell comprising the expression vector of claim 37, Claim 39 specifies a mammalian host cell. Claim 42 is drawn to a host cell comprising the expression vector of claim 41. Claim 43 specifies a mammalian host cell. The specification states on page 72, line 14 to page 75, line 3 that the isolated nucleic acids of pyrin 5 can be used in gene therapy. On page 75, line 4 to page 79, line 10 that the isolated nucleic acids encoding pyrin-5 can be used to create a non-human transgenic animal. Neither of these uses are enabling by the specification for the following reasons:

(A) As drawn to gene therapy

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp.

239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not

involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B)As drawn to a transgenic animal

The specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287, see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genome, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

Amendment of the claims to recite "isolated recombinant polynucleotide" , and "isolated cell" and would overcome this rejection.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 5, 28-33 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Ramkumar et al (WO 02/48362, priority to 60/249,401, filed November 15, 2000).

Claim 5 is drawn to an isolated nucleic acid molecule that hybridizes to a nucleotide sequence consisting of SEQ ID NO:5 under conditions of incubation at 45 degrees in 6.0X SSC followed by washing in 0.2X SSC/0.1% SDS at 65 degrees. Claim 28 embodies the nucleic acid of claim 5 wherein the nuclei acid comprises at least 600 nucleotides. Claim 29 comprises the nucleic acid of claim 5 wherein the nuclei acid comprises at least 1000 nucleotides. Claim 30 is drawn to an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising amino acid residues 1-91, 188-506 or 688-1056 of SEQ ID NO:6. Claims 31, 32 and 33 embody the nucleic acid of claim 30 wherein the polypeptide comprises amino acid residues 1-91, 188-506 and 688-1056 of SEQ ID NO:6, respectively.

Ramkumar et al disclose Sequence identifier 3 consisting of at least 1000 nucleotides which would hybridize to the instant SEQ ID NO:5. Said Sequence Identifier 3 encodes a polypeptide which comprise residues 1-91, 188-506 and 688-1056 of SEQ ID NO:6.

10. Claim 11 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/26/2004

Karen A Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER